

Randomised controlled trial of nasal decongestants versus placebo to prolong treatment free periods from continuous positive airway pressure therapy in mild to moderate obstructive sleep apnoea (DOSA)

Statistical Analysis Plan

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CONTENTS

1. INTRODUCTION	3
1.1 KEY PERSONNEL.....	3
2. BACKGROUND AND OBJECTIVES.....	4
2.1 BACKGROUND AND RATIONALE	4
2.2 OBJECTIVES	5
3. STUDY METHODS.....	5
3.1 TRIAL DESIGN/Framework	5
3.2 RANDOMISATION AND BLINDING.....	5
3.3 SAMPLE SIZE	6
3.4 STATISTICAL INTERIM ANALYSIS, DATA REVIEW AND STOPPING GUIDELINES	6
3.5 TIMING OF FINAL ANALYSIS	6
3.6 BLINDED ANALYSIS	6
4. STATISTICAL PRINCIPLES.....	6
4.1 STATISTICAL SIGNIFICANCE AND MULTIPLE TESTING	6
4.2 DEFINITION OF ANALYSIS POPULATIONS	6
5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES	7
5.1 REPRESENTATIVENESS OF STUDY SAMPLE AND PATIENT THROUGHPUT	7
5.2 COMPARISONS OF LOSSES TO FOLLOW-UP.....	7
5.3 BASELINE COMPARABILITY OF RANDOMISED GROUPS.....	7
5.4 QUALITY CONTROL AND DATA VALIDATION.....	7
6. ANALYSIS.....	7
6.1 OUTCOMES	7
6.2 GENERAL ANALYSIS CONSIDERATIONS.....	8
6.3 ADJUSTMENTS	8
6.4 PRIMARY ANALYSIS OF PRIMARY OUTCOME	8
6.5 SENSITIVITY ANALYSES OF PRIMARY OUTCOME	9
6.6 PRE-SPECIFIED SUBGROUP ANALYSES OF PRIMARY OUTCOME	9
6.7 ANALYSES OF SECONDARY OUTCOMES	9
6.8 HARMS	9
7. SPECIFICATION OF STATISTICAL PACKAGES	9
8. REFERENCES	10
9. APPENDIX: GLOSSARY OF ABBREVIATIONS	11
10. CHANGES FROM PREVIOUS VERSION OF SAP	11
11. EXAMPLE TABLES TO REPORT TRIAL RESULTS.....	12

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the randomised controlled trial of the use of nasal decongestants in obstructive sleep apnoea (DOSA). The SAP has been drafted with reference to the SAP Guideline¹, the CONSORT statement² and ICH E9 Guidelines³.

The results reported in these papers should follow the strategy set out here. Any subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis will be carried out by an identified, appropriately qualified and experienced individual, who will ensure the integrity of the data. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

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2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

The full background and rationale for the trial is provided in the detailed protocol. In brief, DOSA is a double-blinded randomised controlled trial to assess the ability of nasal decongestants to enable patients with obstructive sleep apnoea (OSA) to temporarily suspend their use of CPAP. Patients have often voiced the desire to “take a break” from their CPAP, and it has previously been shown that this may be feasible without an immediate return to OSA.

It is thought that one of the relevant factors influencing the return of OSA post CPAP withdrawal is pharyngeal oedema. Nasal decongestants improve nasal flow by vasoconstricting blood vessels and reducing tissue fluid content, shrinking the volume of the mucosa. Thus this action on the nasal and pharyngeal mucosa may delay the return of OSA after stopping CPAP therapy.

2.2 Objectives

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the effect of Xylometazoline versus placebo on the time to return of OSA in patients with mild to moderate OSA following withdrawal of CPAP therapy	Number of days to a return of OSA (ODI >15 on 3 consecutive nights by remote oximetry data or the patient restarts CPAP for recurrence of symptoms.)	Overnight every night pulse oximetry during 28 day treatment/CPAP withdrawal.
Secondary Objectives To assess the effect of Xylometazoline versus placebo on subjective daytime sleepiness in patients with moderate OSA following withdrawal of CPAP therapy To assess the effect of Xylometazoline versus placebo on sleep fragmentation in patients with mild to moderate OSA following withdrawal of CPAP therapy	The change in Epworth sleepiness score, a validated measure of daytime sleepiness Overnight pulse rate rises of more than 6 bpm per hour as a marker of autonomic arousal during sleep fragmentation.	Patient reported sleepiness on ESS score at baseline, and weekly (day 0, 7, 21 and 28), day of CPAP restart and day 7 post CPAP restart Overnight every night pulse oximetry during 28 day withdrawal of CPAP

3. STUDY METHODS

3.1 Trial Design/framework

Multi-centre, parallel-group, double-blinded, individually one-to-one randomised controlled superiority trial comparing the effect of Xylometazoline and placebo nasal/throat spray on the time to return of OSA in patients with mild to moderate OSA on withdrawal of CPAP therapy.

3.2 Randomisation and Blinding

Patients will be identified for randomisation according to the eligibility criteria outlined. Once the patient has given consent to the trial, baseline forms are completed prior to randomisation. The randomisation process will use an online web-based randomisation system provided by Sealed Envelope. Randomisation will be performed using minimisation based on age ($\geq$ vs <60), BMI ($\geq$ vs <37) and trial centre.

Trial participants and investigators will be blinded to the treatment allocation. The randomisation service provides a facility for emergency unblinding of treatment allocation which can be accessed by the local PI in the event of clinical need. Non-emergency unblinding can be requested via the Sealed Envelope system and will require approval by the Chief Investigator.

3.3 Sample Size

From our previous data the relapse of OSA in an untreated group at 2 weeks is 85% (15% do not relapse, ie they 'survive' CPAP withdrawal). By four weeks we assume this will be 10% 'surviving'. We estimate that an absolute improvement of 15% in the number 'surviving' at the end of the study period, i.e. to 25%, would be clinically useful. These survival percentages imply a hazard ratio of 0.60 (assuming an exponential distribution for relapse time) which, for 90% power, requires a total sample size of 208 patients based on a simple logrank test. If we assume a withdrawal rate of 10% this comes to a total of 232 subjects required.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

No interim statistical analysis is planned.

3.5 Timing of Final Analysis

The statistical analysis will be undertaken after the final data have been collected for each participant (ie following the final visit 2) and the database locked.

3.6 Blinded analysis

The data will remain blinded until completion of the trial. Statistical analysis will be completed with groups identified by randomly assigned arbitrary identifiers (group 0 and group 1). Only on completion of the planned statistical analysis and discussion and interpretation of the results at the Trial Management Group will these groups be unblinded.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

All significance tests and confidence intervals will be reported using a 5% significance level. There will be no statistical adjustments for multiplicity.

4.2 Definition of Analysis Populations

The ***intention to treat (ITT) population*** will include all patients randomised, irrespective of whether they received any trial intervention. As per usual statistical convention for superiority studies, the ITT population will form the primary analysis population.

The ***per-protocol (PP) population*** will only include patients who are randomised and are protocol adherent. Patients will be assessed as protocol adherent if they meet ALL the following criteria:

- Completed Visit 1 and Visit 2 assessments
- Used nasal and throat spray for greater than 70% of expected nights as assessed by returned spray bottle weight OR electronic diary record
- Overnight oximetry data is available for at least 1 night if return to CPAP occurred at/prior to night 3 off CPAP; OR overnight oximetry data is available for >50% of nights off CPAP if return to CPAP occurred later than night 3.
- No significant protocol deviations are reported. Protocol deviations as a result of patients delaying the start date of the expected off-CPAP period will not cause exclusion as long as the actual start date of the off-CPAP period is known. Adjustments will be made to calculate the number of days until the primary outcome is reached (return to CPAP) from the actual start date.

The **safety population (SP)** will include all patients who have used the nasal and throat spray. This will include all patients who have collected the sprays from the pharmacy unless they meet ALL of the following criteria:

- report never having used the sprays during the Visit 2 interview
- the electronic diary reports no usage of the sprays
- the weight of the returned spray bottles is within 0.05g of standard starting bottle weight

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

Patients assessed for eligibility, reasons for exclusion, those randomised and the flow of patients through the study will be described in the CONSORT flow diagram (*Figure 1*).

If any ineligible patients are randomised, numbers and reasons will be reported.

5.2 Comparisons of losses to follow-up

The numbers (percentages) of patients lost to follow up and withdrawn throughout the study will be reported within each treatment group. These data will be described in the CONSORT flow diagram.

5.3 Baseline Comparability of Randomised Groups

Within each of the two randomised groups baseline characteristics will be described. These will include sex, age, BMI, severity of OSA (4% ODI), average use of CPAP (hours per night), time since started CPAP therapy, neck circumference, Mallampati score, smoking status and co-morbidity (*Figure 2*).

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

5.4 Quality Control and Data Validation

Day-to-day monitoring of the trial will be carried out by ORTU, which is responsible for data entry and validation. Its staff will maintain regular contact with site personnel to check on progress and deal with onsite queries. Following database lock, the data will be sent to the trial statistician who may raise any subsequent queries, as may be identified through the analyses, with the ORTU for resolution.

6. ANALYSIS

6.1 Outcomes

Outcomes will be collected from several sources: clinical measures and participant-completed questionnaires at visits 1 and 2, overnight pulse oximetry data and participant-completed daily electronic diaries.

Time to return of Obstructive Sleep Apnoea (primary outcome)

- 1) The primary outcome measure is the number of days to return of OSA. This is triggered if and when the participant's overnight oximetry shows 3 consecutive nights with a 4% ODI of greater than 15 events per hour or the participant self-initiates a return to CPAP therapy. If the participant has still not returned to CPAP at 28 days, s/he is considered censored at that time for the purpose of analysis. Only complete nights without a return to CPAP therapy will be counted. Nights with missing oximetry data are assumed to have shown an ODI of >15 and treated accordingly. However,

if a recommendation to return to CPAP is triggered by 3 consecutive qualifying nights but the **last** of these 3 nights is missing, then a blinded review committee will examine the available data to decide whether a return to OSA is indicated (triggering the primary outcome) or that this cannot be determined (the patient is then “censored” at night 3).

Daytime sleepiness

Daytime sleepiness is captured through the Epworth Sleepiness Scale⁴ and the Karolinska Sleep Scale⁵, both subjective measures reported by the participant. The ESS is recorded at baseline and then every 7 days while the participant remains off CPAP, and finally at day 35 **or** 7 days after resuming use of CPAP. The KSS is recorded daily while the participant remains off CPAP.

Sleep fragmentation

Overnight pulse rate rises of more than 6 bpm per hour will be used as a marker of autonomic arousal during sleep fragmentation, captured through the overnight oximetry data while the participant remains off CPAP.

Quality of life

Quality of life is captured through the Sleep Apnoea Quality of Life Index⁶ (SAQLI; which has four domains) and SF-36 (eight domains) questionnaires. For the purpose of economic evaluation, the EQ-5D-5L is also completed; it will be scored using the crosswalk mapping tool to UK value sets. These questionnaires are self-completed by the participant at visit 1 (baseline) and at visit 2.

Blood pressure

Blood pressure is measured at visits 1 and 2.

6.2 General analysis considerations

Wherever possible, analyses will be presented with 95% confidence intervals and all reported p-values will be two-sided, unless otherwise stated. Summary descriptive data will be presented as numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables. Where necessary, transformations of variables will be considered, eg for the purpose of enabling closer approximation to a normal distribution or to stabilise variances. Unless otherwise stated, analyses will use the ITT population. Sensitivity analyses may use the per-protocol population as indicated. Safety analyses will use the safety population.

6.3 Adjustments

Unless otherwise stated, all comparative analyses will adjust for the minimisation variables of age ($\geq$ vs <60), BMI ($\geq$ vs <37) and centre. Given the small number of centres, a fixed effect will be used.

6.4 Primary analysis of primary outcome

The primary outcome will be presented as a survival analysis (time to event) Kaplan-Meier curve. Primary analysis will use a Cox regression model to estimate the hazard ratio with 95% confidence intervals. Appropriate assessments will first be made to check the assumptions underpinning a Cox regression model. The median time to return of OSA will be reported for each group from the fitted model. A second analysis will be based on a simple uncorrected logrank test comparing the two groups. As far as possible the ITT principle will be followed, although analysis will be based on complete cases – that is, participants will be excluded if there is no assessment available for the occurrence of the primary outcome.

6.5 Sensitivity analyses of primary outcome

A secondary analysis will be conducted using the per-protocol population, otherwise using the same approach as above.

The nature of any missing data will be assessed to determine possible additional sensitivity analyses. Baseline values will be summarised for those with and without missing data for the primary outcome to describe any characteristics related to missingness that are able to be observed. Reasons for missingness will be presented where available. If there is a difference in the amount of missing data between the two arms, sensitivity analysis will be used to examine best case and worse case scenarios. Multiple imputation will be considered if the necessary assumptions appear to be reasonable, including in particular whether the data are likely to be missing at random.

6.6 Pre-specified subgroup analyses of primary outcome

The study is not powered to perform formal subgroup analyses, but a number of exploratory such analyses will be performed. Each such analysis will include main effects for treatment group and the variable related to the subgroup of interest, plus an interaction term for those two variables. Only if the interaction term is significant will the subgroups be analysed and presented separately. Subgroup analyses of the primary outcome will be carried out for BMI (BMI>30, BMI<30), smokers/non-smokers, severity of OSA (4% ODI 15-25 and 25-30) and CPAP usage at baseline (below and above the median hours use at baseline).

6.7 Analyses of secondary outcomes

Secondary outcomes will be analysed with an appropriate regression model (following transformation of data as may be appropriate) including a term for treatment effect and the minimisation variables as covariates. For outcomes where the baseline value of the outcome is captured, it will also be included as a covariate. All such analyses will be conducted on the ITT population, but omitting cases for whom there are no outcome data available.

The **Epworth Sleepiness Scale** is captured weekly while the participant remains off CPAP, then at one week following return to CPAP (which may be at 28 days or earlier). A mixed-effects (multilevel) linear model will be used to reflect the repeated measures nature of these data. Included in the model will be a term for whether the patient has been on CPAP or not in the previous week. Likewise, the **Karolinska Sleep Scale** is captured daily while off CPAP and again a mixed-effects linear model will be used. **Sleep fragmentation** is captured by nightly counts of pulse rate rises of more than 6 bpm per hour and will also be analysed by mixed-effects models, possibly Poisson or negative-binomial according to the nature of the data.

Quality of life data (SAQLI, SF-36, EQ-5D-5L) and blood pressure are all measured at the two visits, and will be analysed using analysis of covariance assessing treatment effect at visit 2 while controlling for baseline.

6.8 Harms

This analysis will be based on the safety population. The number and percentage of patients to have experienced an adverse event (AE), a serious adverse event (SAE), or complication will be reported for each group. Categorisation will be undertaken by an independent reviewer and will include a judgement as to whether the event was related to use of the sprays, CPAP withdrawal or unrelated.

7. SPECIFICATION OF STATISTICAL PACKAGES

All analyses will be carried out using the latest available version of STATA.

8. REFERENCES

1. Gamble, C., et al., Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA, 2017. 318(23): p. 2337-2343
2. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332
3. ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9. 1998.
4. ESS
5. KSS
6. SAQLI

9. APPENDIX: GLOSSARY OF ABBREVIATIONS

CPAP	Continuous Positive Airways Pressure
ESS	Epworth Sleepiness Scale
KSS	Karolinska Sleep Scale
ODI	Oxygen desaturation index
ORTU	Oxford Respiratory Trials Unit
OSA	Obstructive Sleep Apnoea
SAP	Statistical Analysis Plan
SAQLI	Sleep Apnoea Quality of Life Index
TSC	Trial Steering Committee

10. CHANGES FROM PREVIOUS VERSION OF SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons

11. EXAMPLE TABLES TO REPORT TRIAL RESULTS

Figure 1: Consort Diagram

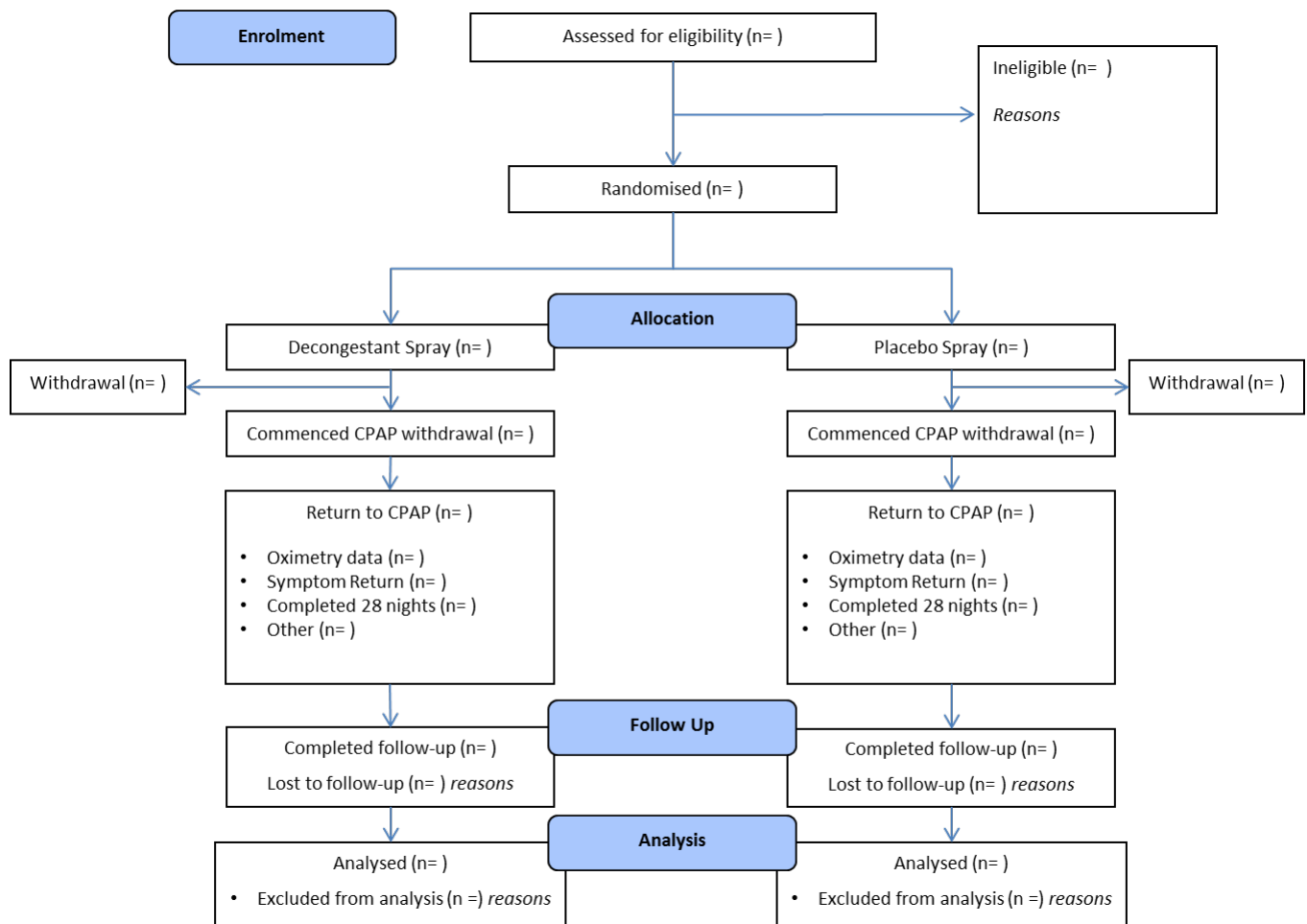


Figure 2: Baseline Characteristics of Trial Participants

	Placebo Spray (n=)	Decongestant Spray (n=)	Overall (n=)
Age (years)^a			
Sex			
Male (N, %)			
Female (N, %)			
OSA Diagnostic Test			
Oximetry (N, %)			
4% ODI, events per hour ^a			
CPAP Data			
CPAP Pressure, cmH ₂ O ^a			
CPAP Usage, hours/night ^a			
Days since CPAP Commenced ^b			
Other Baseline Characteristics			
Current Smokers (N, %)			
BMI, kg/m ² ^a			
Neck Circumference, cm ^a			
Mallampati Score (N(%) in each score 1–4)			
Recruiting Site			
Site A (N, %)			
Site B (N, %)			
Co-morbidities			
Heart disease (N, %)			
Hypertension (N, %)			
Stroke (N, %)			
Diabetes (N, %)			
Anxiety/Depression (N, %)			
Insomnia (N, %)			

^aMean (SD) ^bMedian (IQR)

Figure 3: Primary Outcome Analysis

	Placebo Spray	Decongestant Spray
Median Number of Days until CPAP return		
Reason for return to CPAP		
3 consecutive nights ODI >15 (N, %)		
Patient Initiated, symptom return (N, %)		
Completed 28 nights off CPAP (N, %)		

	Adjusted*		Unadjusted	
	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value
Primary analysis				
Sensitivity analysis using per protocol population				
Other sensitivity analyses				

* adjusted for all minimisation variables

Figure 4: Secondary outcome analyses: SF-36

	Decongestant		Placebo		Adjusted comparison	
	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Mean difference (95%CI)	p-value
Physical functioning						
Role functioning/physical						
Role functioning/emotional						
Energy/fatigue						
Emotional well-being						
Social functioning						
Pain						
General health						
Overall						

Figure 5: Secondary outcome analyses: SAQLI

	Decongestant		Placebo		Adjusted comparison	
	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Mean difference (95%CI)	p-value
Daily functioning						
Social interactions						
Emotional functioning						
Symptoms						

Figure 6: Secondary outcome analyses: ESS

	Decongestant		Placebo		Adjusted comparison	
	Mean (SD)		Mean (SD)		Treatment effect (95%CI)	p-value
Day 0					-	-
Mean for days off CPAP					-	-
7 days following return to CPAP					-	-